IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., and CIMA LABS, INC.	)	
Plaintiffs,	)	
v.	)	Civ. No. 09-724-SLR
WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., and WATSON PHARMA, INC.,	)	
Defendants.	)	

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OPINION

Dated: March 24, 2011
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

Plaintiff Cephalon, Inc. ("Cephalon") is the owner of U.S. Patent No. 6,264,981 ("the '981 patent"). Cephalon is the holder of an approved New Drug Application ("NDA")[1] for the manufacture and sale of fentanyl buccal tablets for the treatment of breakthrough cancer pain. Defendants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Watson Pharma, Inc. (collectively, "Watson") filed an Abbreviated New Drug Application ("ANDA")[2] in 2008 for a generic version of Fentora® (fentanyl buccal tablets). Cephalon and plaintiff CIMA Labs, Inc. ("CIMA"), Cephalon's wholly-owned subsidiary, sued Watson for infringement of U.S. Patent Nos. 6,200,604 ("the '604 patent") and 6,974,590 ("the '590 patent") (collectively, the "Khankari patents"), which patents were listed in the Orange Book in connection with Cephalon's NDA.[3] (Civ. No. 08-330, D.I. 1) Plaintiffs later brought suit for infringement of the '981 patent. (Civ. No. 09-724) The cases were consolidated for purposes of discovery and a bench trial, which was held between May 10 and 17, 2010. The court references its recent decision on the Khankari patents for the relevant procedural history. (Civ. No. 08-330, D.I. 327) The court turns now to the issues of infringement and validity of the '981 patent, which have been fully briefed post trial. The court has jurisdiction pursuant

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[1]No. 21-947.

[2]No. 79-075.

[3]Watson's ANDA contained a paragraph IV certification as to the Khankari patents. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 35 U.S.C. § 271(e)(2)(A) ("(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]").

to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. The '981 patent describes improved oral transmucosal drug formulations using a solid solution. Drs. Hao Zhang ("Zhang") and Jed Croft are named as inventors. The '981 patent was filed on October 27, 1999 and issued July 24, 2001; no earlier priority is claimed. The original assignee, Anesta Corporation ("Anesta"), was acquired by Cephalon in August of 2000. (D.I. 149 at 58:14-18)[4]

2. The '981 patent discusses the difficulty in formulating a drug for oral mucosal delivery in view of the solubility/absorbability balance. ('981 patent, col. 4:14-23; col. 4:53-63) The disclosed invention is a drug in solid form combined, at a molecular level, with a dissolution agent also in solid form, yielding a solid solution. (*Id.*, col. 5:40-45; col. 6:35-39; col. 6:67-col. 7:4) The pharmaceutical agent selected for delivery, which may be "any drug substance," determines the selection of the appropriate dissolution agent (that can mix with that drug at the molecular level). (*Id.*, col. 6:44-col. 7:10) The

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[4]All D.I. numbers hereinafter refer to Civ. No. 09-724, unless otherwise noted. For ease of reference, the bench trial transcript was docketed at D.I.s 149-154 in Civ. No. 09-724, and it correlates to D.I.s 282-287 in Civ. No. 08-330. Infringement briefs referred to in the prior opinion (Civ. No. 08-330, D.I.s 244, 253 and 262) are docketed in this action as D.I.s 111, 120 and 129. Validity briefs referred to in the prior opinion (Civ. No. 08-330, D.I.s 245, 251 and 261) are docketed in this action as D.I.s 112, 118 and 128. Claim construction materials correlate as follows: opening briefs (Civ. No. 08-330, D.I.s 193, 194 with Civ. No. 09-724, D.I.s 56, 59); answering briefs (Civ. No. 08-330, D.I.s 210, 211 with Civ. No. 09-724, D.I.s 80, 81); and joint appendices (Civ. No. 08-330, D.I. 197 (all volumes) with Civ. No. 09-724, D.I. 58 (same)).

process to be used is also considered in the selection of a dissolution agent, and may include a variety of well-known processes such as wet granulation, partial wet granulation, co-melting, freeze drying, and spray-drying. (*Id.* at col. 8:45-50) The '981 patent discloses that the solid solution of the invention provides for an increased dissolution rate, a higher solubility and, uniquely, stabilization of the drug in solid formulation. (*Id.* at col. 8:51-col. 9:31) The specification also provides that, "[i]n order for the present invention to operate effectively, it is necessary that the drug incorporated within the dissolvable matrix be capable of permeating the mucosal membrane either alone or by suitable adjustments in the environmental pH, or other chemical modification or in combination with a suitable permeation enhancer." (*Id.*, col. 9:32-37) Thus, other pharmaceutical ingredients (such as buffering agents) may be included in the formulation of the invention. (*Id.*, col. 11:25-37)

3. Watson's ANDA product contains fentanyl citrate, potassium bicarbonate, mannitol, sodium starch glycolate ("SSG"), and magnesium stearate. (D.I. 150 at 280:17-281:1; DTX-1456 at 9992) Watson's ANDA product includes 100, 200, 300, 400, 600 and 800 µg fentanyl buccal tablets. Each tablet strength is qualitatively identical; quantitatively, the formulations differ only with respect to the amounts of fentanyl citrate and mannitol. (D.I. 150 at 257:2-11, 280:17-281:1; PTX-229) The 100 µg tablet is also 50% smaller. (*Id.*)

4. Cephalon asserts that Watson's ANDA product infringes claims 3, 5, 32 and 54 of the '981 patent. The '981 patent contains three independent claims, each of which are relevant to the present suit. Claim 1 provides a solid dosage form, as follows:

1. An improved oral transmucosal solid dosage form drug delivery

formulation comprising:

a pharmaceutical agent capable of being absorbed into oral mucosal tissue having a dissolution rate in the solvents found in the oral cavity,

a dissolution agent having a dissolution rate in the solvents found in the oral cavity, said dissolution rate of said dissolution agent being greater than said dissolution rate of said pharmaceutical agent, and said pharmaceutical agent being in solid solution with said dissolution agent.

Claim 3 depends from claim 2 (depending further on claim 1) and requires that the formulation comprises a buffer system that "is capable of maintaining a significant portion of said pharmaceutical in an unionized form following dissolution of said pharmaceutical agent." Claim 5 depends from claim 1 and further requires that the dissolution agent "provides a physical barrier between pharmaceutical agent and said buffer while in storage."

5. Independent claim 30 provides a method for delivery of a solid solution, as follows:

30. A method for oral transmucosal delivery of a pharmaceutical agent comprising the steps of:

providing a drug formulation comprising a solid pharmaceutical agent in solid solution with a dissolution agent,

administering said drug formulation into a patient's oral cavity, and

delivering said pharmaceutical agent by absorption through a patient's oral mucosal tissue.

Asserted claim 32 depends from claim 30 and further requires that "said butter maintains a pH level such that ionization of said pharmaceutical is controlled by said buffer system."

6. Claim 51 claims a drug formulation, as follows:

51. An oral mucosal drug formulation comprising:

a solid solution micro-environment within the drug formulation,

a drug and a dissolution agent disposed within the solid solution micro-environment, and

a pharmaceutical ingredient segregated from the micro-environment.

Asserted claim 54 depends on claim 51 and further requires that the pharmaceutical ingredient improves absorption of the drug.

B. Claim Construction

1. Standards

7. Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence – the claims, specification and prosecution history – because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips,* 415 F.3d at 1313.

8. Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the

meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. "Solid solution"[5]

9. To provide context for the dispute, an active pharmaceutical ingredient (or "API") can exist in several different solid state forms.[6] APIs exist most often as a crystalline material. (D.I. 151 at 594:6-595:13) A crystalline API possesses long range order, where drug molecules are arranged in a regular, ordered fashion. (*Id.* at 594:6-595:4; 591:6-11) Crystalline APIs can potentially exist in different crystalline forms, including polymorphs and hydrates. (*Id.* at 594:6-12; 598:9-599:3; 638:4-8.) Polymorphs occur when the drug molecules have a particular crystal arrangement that differs from the original crystalline arrangement. Hydrates occur when water molecules are arranged among drug molecules in a crystal structure. Hydrates can have different degrees of hydration, for example, monohydrates, dihydrates, and so on, depending on the relative amount of water molecules to drug molecules in the crystal structure. (*E.g.*, *id.* at 639:6-15) A crystalline API with no water molecules within its structure is

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[5]Watson did not object to Cephalon's discussion of these principles or pose any contrary findings of fact thereon and, therefore, the court adopts Cephalon's discussion of the solid state chemistry.

[6]As noted *supra* (¶ 2), the specification uses "pharmaceutical agent" synonymously with "drug" to be delivered across the oral mucosa. ('981 patent, col. 5:40-45, col. 6:44-45) The court hereinafter will frame its discussions according to the terms used in the claims being discussed, whether "pharmaceutical agent" (claims 3, 5, 32) or "drug" (claim 54). In both contexts, the relevant ingredient here is fentanyl citrate, which is also an "API" as described by the parties.

Notably, however, "pharmaceutical ingredient" is used in the '981 patent not to denote the drug to be delivered across the oral mucosa, but generally to describe other ingredients such as buffers. (*Id.*, col. 7:21-23, col. 11:25-37) To avoid confusion, although the parties refer to fentanyl citrate as the "API" in their papers, the court will, in its analysis hereinafter, reference fentanyl as a "drug" or "pharmaceutical agent" as recited by the claims.

sometimes referred to as an anhydrous drug. (*Id.* at 641:14-21) Finally, crystals can be a range of sizes, including relatively small nanocrystals. (*Id.* at 620:12-16)

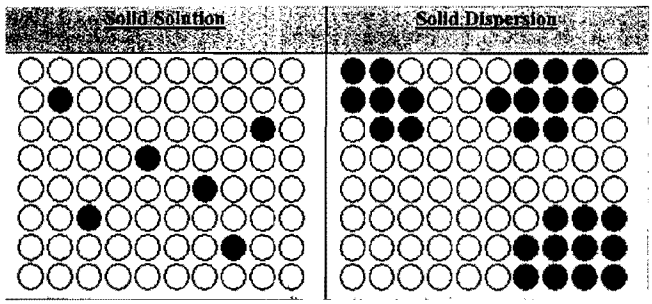
10. APIs can also exist as an amorphous material. (*Id.* at 594:13-17) An amorphous API is disordered, lacking the long-range order found in crystalline drugs. (*Id.* at 594:22-595:4) Although amorphous APIs often have beneficial properties relative to their crystalline counterparts, they currently are uncommon in pharmaceutical products because they tend to be difficult to make and because they are unstable. (*Id.* at 595:5-13.) Amorphous drugs are prone to convert back into the more stable crystalline form. (*Id.* at 584:16-18)

11. Finally, APIs can also exist in a solid solution with another component. In contrast to both crystalline and amorphous drugs— which are pure phases consisting of many drug molecules associated in either an ordered (crystalline) or disordered (amorphous) fashion— a solid solution occurs when there is molecular-level mixing between the API and another component. ('981 patent, col. 8:45-47) Solid solutions often have similar benefits to amorphous drug forms, but in a form that can be stable and, therefore, resistant to recrystallization. (D.I. 151 at 584:6-18)

12. The parties dispute whether Watson's ANDA product contains a "solid solution" as required by each of the asserted claims of the '981 patent, as well as whether the prior art discloses the claimed "solid solution." The parties propose the following constructions for the term.

Disputed Claim Term	Cephalon's Proposed Construction	Watson's Proposed Construction
"solid solution"	"a solid phase consisting of at least a dissolution agent and an active ingredient that are mixed at the molecular level"	"the pharmaceutical agent and dissolution agent are mixed at the molecular level such that the individual molecules are dispersed in the solid state"

Although the parties agree that the solid solution requires a pharmaceutical or active agent and a dissolution agent that are "mixed at the molecular level,"[7] Watson adds the further limitation that the mixture at the molecular level be "such that the individual molecules are dispersed in the solid state." That is, "individual pharmaceutical agent molecules are (or nearly are) separated from one another and exist dispersed among the dissolution agent's molecules." (D.I. 59 at 32) Watson seeks to distinguish a solid dispersion, wherein large aggregates of molecules of pharmaceutical agents are dispersed among particles of dissolution agent in the solid state, as illustrated by the following:



[7]This is supported by the specification, which provides that: (1) "[t]he solid solution formulation comprises a pharmaceutical agent or drug capable of being delivered via the oral mucosal membrane and a dissolution agent(s) capable of being mixed with the pharmaceutical agent at the molecular level" ('981 patent, col. 6:35-39); (2) the end result is "a finely blended mixture in which the drug and the dissolution agent are mixed at the molecular level" (*id.*, col. 7:49-53); and (3) "[t]here are many other process for making [a] solid solution of drug and dissolution agent, (i.e. processes that mix the drug and dissolution agent at the molecular level)" (*id.*, col. 8:45-47).

(*Id.* at 32-33)

13. Watson relies in its papers on portions of the specification stating that the drug and dissolution agent are mixed at the molecular level, which does not speak to the additional limitation Watson seeks. That the specification refers to a "finely blended mixture" does not speak to the nature of the dispersion. (*Id.* at 33 (citing '981 patent, col. 7:36-53))

14. At trial, Zhang offered the following:

> [A] solid solution is a term that people use very loosely. People use solid solution, others use solid dispersion. If you ask different people, they may give you different answers. Some people actually believe the solid dispersion is the same as the solid solution. . . That is why in my patent I tried to define very clearly what is a solid solution, so that the definition in my patent of a solid solution is a molecular level mix of two or three or more ingredients.

(D.I. 151 at 542:4-19)

15. On the foregoing record, the court declines to limit the claims to exclude a solid dispersion, as characterized by Watson in its briefs. Watson has not cited any intrinsic (or extrinsic) evidence showing that a person of ordinary skill in the art in 1999 would have interpreted a "solid solution" as described by the '981 patent as excluding a "solid dispersion." (D.I. 59) The foregoing testimony by Zhang[8] is not intrinsic evidence and was not vetted during discovery. For the foregoing reasons, the court construes "solid solution" as a mixture in which at least a pharmaceutical agent and a dissolution agent are mixed at the molecular level. The court finds no occasion to further limit the term to a particular degree of molecular mixing.

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[8]Solicited, the court notes, on cross-examination.

3. "Solid solution micro-environment"

16. Cephalon proposes that "solid solution micro-environment within the drug formulation" means that the drug formulation consists of a "**solid solution** that is segregated from the other component(s) of the formulation." Watson asserts that the term be construed to mean "the environment within the solid solution where the **pharmaceutical agent** resides segregated from the rest of the formulation and the overall environment." (D.I. 49)

17. The '981 patent provides that the

> invention may also provide for a way to stabilize the drug in the solid formulation. Because the drug is processed and resides in [a] micro-environment within the whole drug formulation, it is possible to create a favorable micro-environment to promote drug stability, and to promote absorption of the drug by using the rest of [the] formulation to create a favorable environment for drug absorption. Thus the solid solution drug formulation facilitates stability without compromising drug delivery. The segregated solid formulation is therefore a unique advantage of this invention.

('981 patent, col. 9:22-32) Claim 51, from which claim 54 depends, separately describes a "solid solution micro-environment" and that a "pharmaceutical ingredient [is] segregated from the micro-environment." That is, claim 51 describes a portion of the drug formulation that is a solid solution (the micro-environment) wherein the "drug" is contained, and a portion of the drug formulation that is not a solid solution that contains a pharmaceutical ingredient to promote absorption.

18. Given the above, the court construes this limitation, the "solid solution micro-environment within the drug formulation," to mean that the "drug formulation comprises a solid solution containing the drug (pharmaceutical agent) to be delivered. The solid solution is segregated from other component(s) of the formulation."

4. "Buffer system"

19. The parties did not ask the court to construe "buffer" or "buffer system" as used in the '981 patent.[9] (D.I. 49) Nevertheless, the court must attribute meaning to the terms in order to resolve the infringement and validity disputes as presented by the parties.

20. With respect to infringement, Cephalon asserts that the potassium bicarbonate in Watson's ANDA tablets meets the "buffer system" limitation of claim 3 because it is an amphoteric substance, meaning that it can (itself) act as an acid or a base. (D.I. 111 at 50 (citing D.I. 151 at 741:13-743:8)) Watson argues that potassium bicarbonate cannot be a "buffer system" in view of the '981 patent specification, providing that

> a buffer system consists of hydrogen acid donor(s) (acid) and conjugate hydrogen ion receiver(s) (base). An appropriate buffer system stabilizes the pH. However, optimizing the pH generally compromises the solubility and partition coefficient for oral transmucosal drug delivery.

('981 patent, col. 4:65-col.5:3)

21. The '981 patent identifies "buffering agents (such as phosphate buffer[])" as an example of a pharmaceutical ingredient that may be contained in the formulation of the invention. ('981 patent, col. 11:25-27) The specification also generally provides that "[t]he solid solution formulation may be further combined with buffers and other excipients as needed in order to facilitate the drug's manufacturing, storage, administration and delivery through oral mucosal tissue." (*Id.*, col. 5:44-48)

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[9]Indeed, the issue was given little attention by the parties in their post-trial briefing.

(emphasis added) It is not clear from the foregoing whether the buffers facilitate manufacturing, etc., or whether this function may be performed by other excipients, or both.

22. There is no further use of the term "buffer" (alone) outside of the claims. Claim 2 adds a "buffer system" limitation to the formulation of claim 1. Claim 4, which depends on claim 2, states as follows:

> The formulation system of claim 2, wherein a for said **system** is chosen from the group consisting of: **phosphate**, carbonate, tris, tartrate, borate, acetate, or maleate **buffer**.

(*Id.*, col. 15:12-14) (emphasis added) The syntax of claim 4 implies that a "buffer" may also be a "buffer system."

23. Claim 32 depends from claim 30, which does not contain either "buffer" or "buffer system" term. Yet claim 30 provides as follows:

> 32. The method of claim 30, wherein said **buffer** maintains a pH level such that ionization of said pharmaceutical is controlled by said **buffer system**.

(*Id.*, col. 17:20-22) (emphasis added) That is, the term "said buffer" as used in claim 32 has no antecedent basis in claim 30. Dependant claim 5 also refers to "said buffer," which has no antecedent basis in claim 1, from which it depends. Watson raises a 35 U.S.C. § 112, ¶ 4[10] validity defense based on this improper dependency.

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[10]Section 112, ¶ 4 of the patent code provides that

> a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

35 U.S.C. ¶ 112, ¶ 4.

24. Most notably, the parties in this case agree that claims 5 and 32 contain typographical errors that should be corrected as follows: claim 5 should depend from claim 2 (not claim 1); and claim 32 should depend from claim 31 (not claim 30). (D.I. 151 at 746:1-23, 748:14-19; D.I. 152 at 1017:8-15, 1018:25-1020:6; D.I. 118, ex. 5 (Watson's trial slides))

25. Where no certificate of correction has been issued for a patent, as is the case here, a district court can correct an error through claim construction "only if (1) the correction is not subject to reasonable debate based on consideration of the claim language and the specification; and (2) the prosecution history does not suggest a different interpretation of the claims." *Novo Industries, L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354 (Fed. Cir. 2003); *accord Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1216 n.8 (Fed. Cir. 2008) (the exception to the rule against redrafting claims is "when there is an obvious administrative or typographical error that is not subject to reasonable debate"). Here there is agreement by the parties as to the nature of the mistake, and Watson does not refute Cephalon's representation that the prosecution history does not suggest a different interpretation of the claims. (D.I. 118 at 31; D.I. 128 at 16, n.4) The court construes the claims accordingly.[11] Therefore, the claims recite (by group):

1. An improved oral transmucosal solid dosage form drug delivery formulation

[11]Despite its agreement as to the error of the claims, Watson asserts that it is still within its rights to contest validity under 112 ¶ 4. (D.I. 128 at 16, n.4) Cephalon argues that Watson waived its right to assert the ¶ 4 defense because it did not disclose the defense to Cephalon during discovery and presented it for the first time in its post-trial papers. As the court has construed the claims in accordance with the parties' stipulation, Watson's ¶ 4 defense is moot in either event.

comprising:
a pharmaceutical agent capable of being absorbed into oral mucosal tissue having a dissolution rate in the solvents found in the oral cavity,
a dissolution agent having a dissolution rate in the solvents found in the oral cavity, said dissolution rate of said dissolution agent being greater than said dissolution rate of said pharmaceutical agent, and said pharmaceutical agent being in solid solution with said dissolution agent.

2. The formulation of claim 1 further comprising a **buffer system**.
* * *
5. The delivery system of claim **2**, wherein said dissolution agent provides a physical barrier between pharmaceutical agent and **said buffer** while in storage.

* * *

30. A method for oral transmucosal delivery of a pharmaceutical agent comprising the steps of:
providing a drug formulation comprising a solid pharmaceutical agent in solid solution with a dissolution agent,
administering said drug formulation into a patient's oral cavity, and
delivering said pharmaceutical agent by absorption through a patient's oral mucosal tissue.

31. The method of claim 30, wherein the step of providing a drug formulation further comprises a **buffer system**.

32. The method of claim **31**, wherein **said buffer** maintains a pH level such that ionization of said pharmaceutical is controlled by said **buffer system**.

(emphasis added)

26. As the foregoing indicates, the claims at times refer to a "buffer" and at other times a "buffer system." "When construing terms in the body of a claim, the general assumption is that different terms have different meanings[.]" *See Symantec Corp. v. Computer Associates Intern.*, 522 F.3d 1279, 1289 (Fed. Cir. 2008) (citation omitted). Yet by their stipulation, the parties essentially agree that "buffer" and "buffer system" may be used interchangeably. This is supported by the inventors' description of

"buffering agents" in the specification ("buffering agents (such as phosphate buffer, carbonate buffer, tris buffer, tartrate buffer, borate buffer, acetate buffer, or maleate buffer)") – here, "agents" (plural) may refer to a single "buffer" such as a phosphate buffer. ('981 patent, col. 11:25-29) Where the specification refers to "buffer system" in the context of an acid and base,[12] it does not expressly limit the term in this manner.

27. For the foregoing reasons, the court declines to limit the "buffer system" of claims 5 and 32 to an acid/base couple, as Watson suggests.

C. Infringement

1. Standard

28. A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

29. "Direct infringement requires a party to perform each and every step or

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[12]Consistent with the plain meaning of the modifier "system," or an interacting "group" of objects. *See* http://www.merriam-webster.com/dictionary/system, last accessed March 21, 2010.

element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

2. Claim 3

30. Claim 3 requires a solid drug dosage form comprising, *inter alia*, a pharmaceutical agent in solid solution with a dissolution agent, and a buffer system that "is capable of maintaining a significant portion of said pharmaceutical in an unionized form following dissolution of said pharmaceutical agent." The parties focus their dispute on the "solid solution" and "buffer system" limitations.

a. Solid solution

31. Cephalon asserts that, "[t]o the extent Watson's construction limits a solid solution to situations where only individual molecules of fentanyl are dispersed among dissolution-agent molecules, the Watson tablets literally contain a solid solution because fentanyl will be associated at discrete [s]ites along the starch glycolate polymer chain and, therefore, individual molecules will be dispersed. To the extent Watson's tablets also contain regions where some fentanyl molecules are next to other fentanyl molecules, these particular regions would be a solid solution under the doctrine of equivalents." (D.I. 244 at 51) As the court has adopted Cephalon's claim construction and has not defined "solid solution" to exclude a solid dispersion (i.e., a mixture containing aggregates of fentanyl molecules), the court understands Cephalon's infringement position to be one of literal infringement, and proceeds accordingly.

32. The asserted '981 patent claims require that the drug formulation comprise a pharmaceutical agent in solid solution. Cephalon's infringement evidence is best presented against a backdrop of Watson's manufacturing process.

33. Generally, Watson's process starts with a pre-mixing step, whereby mannitol and SSG are mixed together as a powder. Separately, fentanyl citrate is dissolved in purified water to make fentanyl citrate solution. The fentanyl citrate solution and pre-mix are then mixed in a granulator for fifteen minutes. The product is then dried at 50° C until it has less than 1% retained water. The granulation is next milled and blended with potassium bicarbonate (for 12 minutes) and lastly blended with magnesium stearate (for 6 minutes). The final tablets are formed during a compression step. (D.I.

151 at 713:22-714:19; PTX-162)

(1) Cephalon's evidence

34. Cephalon presented data though its expert, Dr. Simon Bates ("Bates"), an expert in the solid state characterization of drug products.[13] (D.I. 151 at 575:2-576:1) Bates's protocol was to test each individual component of the ANDA product (e.g., potassium bicarbonate) to establish baseline data and, thereafter, move to binary and tertiary (two or three-component) systems. He concluded by testing the ANDA product itself. (*Id.* at 585:25-587:10) Bates used X-ray Powder Diffraction ("XRPD") and differential scanning calorimetry ("DSC") techniques to study these materials. (*Id.* at 587:11-18; 588:5-10)

35. Bates explained that XRPD is a technique in which X-rays are directed towards and refracted by a sample to be analyzed. The ordered molecules in crystalline materials diffract the X-rays in an ordered manner creating a diffraction

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[13]The court denies at this juncture Watson's motion to strike insofar as it relates to Bates's testimony that Watson's tablets contain a solid solution. (D.I. 121) Bates was identified as a solid solutions expert and the relevance of his testimony could not have been unfair surprise to Watson. Although Bates's expert report was purely technical and did not contain an opinion on infringement (D.I. 122, ex. B; D.I. 151 at 623:10-624:1), Watson opened the door to this opinion during Bates's deposition, at which point Bates thoroughly discussed his infringement opinion (D.I. 132 at 90:19-102:1, 107:7-108:5). Watson could have used Bates's deposition testimony as impeachment at trial and, therefore, the court is not inclined to rule that such testimony may be a "shield" but not a "sword."

The court did not explicitly address the remainder of Watson's motion to strike in its prior opinion, that is, Watson's arguments to strike Cephalon's evidence regarding the presence of citric acid in Watson's tablets, and whether citric acid reacts with potassium bicarbonate to produce effervescence. The court denies Watson's motion as moot on these grounds, in view of its prior finding that such evidence would not have been persuasive even had it been appropriately disclosed. (Civ. No. 08-330, D.I. 327 at 30, n. 25 (noting Bates's admission that he did not opine as to whether the ANDA product actually created citric acid in any event))

pattern having a discrete number of sharp peaks, with the specific diffraction pattern being representative of the spatial arrangement of the molecules in the crystal. (D.I. 151 at 589:7-591:11) The disordered molecules in amorphous materials diffract X-rays in a pattern of broad halos rather than sharp peaks. (*Id.* at 591:6-11) The X-ray diffraction pattern is presented as a plot of the relative intensity of the scattered X-ray as a function of scanning angle 2-theta. (*Id.* at 591:12-20)

36. Bates explained that DSC is a technique that monitors energy flow into a sample. (*Id.* at 591:24-592:10) The output from a DSC experiment is plotted as heat flow, a function of temperature. (*Id.* at 602:11-17) The plot may indicate a phase transition, for example, a glass transition (where an amorphous material goes from its glossy, or frozen solid, state to a more dynamic, rubbery state) or the melting of a sample. (*Id.* at 602:22-604:4)

37. Bates's conclusion following XRPD and DSC testing on Watson's ANDA product (the 800 µg tablet) was that "[l]ess than about 15 percent" of the (620 µg by weight) fentanyl citrate is present as crystalline fentanyl citrate. (617:11-619:12; PTX-546A at fig. 51) By process of elimination, Bates opines that the other 85% of the fentanyl citrate is in a "solid solution." That is, Cephalon's position is that this 85% is not in any of the other possible forms of fentanyl citrate. The court will address these arguments in turn.

38. Besides a solid solution, there are at least three forms that the fentanyl citrate in the ANDA product could take: amorphous, anhydrous and monohydrate. First, it is Bates's opinion that the remaining 85% of the fentanyl citrate is not the amorphous form. Bates had difficulty creating amorphous fentanyl citrate for purposes

of his tests. The amorphous fentanyl citrate Bates tested was made by dissolving fentanyl citrate in water and then rapidly removing the water under vacuum or, alternatively, rapid quench cooling. (D.I. 151 at 599:24-600:22) Bates testified that there are no comparable conditions in Watson's process that may force the fentanyl citrate into the amorphous form. (*Id.*)

39. As the above indicates, the amorphous form is unstable. (*Id.* at 600:14-18) Bates conducted his testing on 800 µg ANDA tablets that were over two years old. In his "experience working with amorphous drug products, it is almost impossible to keep them stable in the amorphous state for that period of time without some stabilizing technology." (*Id.* at 615:3-11, 620:21-22)

40. Having determined that the fentanyl citrate in the ANDA product cannot be in amorphous form, Bates addressed the two crystalline forms of fentanyl citrate that could be formed by Watson's process — anhydrous and monohydrate. (*Id.* at 596:21-599:16) The anhydrous form (the form provided by the fentanyl supplier) exhibits several crystalline XRPD peaks, with its largest, characteristic diffraction peak at a scanning angle of 6.4 degrees (2-theta). (*Id.* at 596:21-598:8; PTX-546A at fig. 13) The monohydrate form has its characteristic diffraction peak close to that of the anhydrous, just below 6 degrees. (*Id.* at 598:9-599:11; PTX-546A at fig. 14) These are sharp peaks indicative of a crystalline structure. (D.I. 151 at 589:7-591:11)

41. In an effort to provide context for the graphs generated by the ANDA product itself, Bates collected data on components of the ANDA product. The parties refer to these tests as the "bracketing" experiments, as they were intended to mimic

intermediates in Watson's manufacturing process. XRPD testing on SSG dissolved in water and dried at 50° C, a temperature Watson uses in its process, revealed a broad peak around 20 degrees (2-theta) – a different region than the about 6 degree peaks seen previously for anhydrous fentanyl citrate. (D.I. 151 at 600:23-601:8; PTX-546A at fig. 4) Bates also created a sample that was 5% pre-dissolved fentanyl citrate, by dissolving the fentanyl citrate in water, dripping the solution into SSG, processing by sonication[14] and drying. (D.I. 151 at 606:9-23) The XRPD for this sample showed a minor signal from a crystalline component around 6 degrees and a large signal around 2 degrees (2-theta). (*Id.*; PTX-546A at fig. 21)

42. Bates also performed DSC on the intermediates. The DSC plot for anhydrous fentanyl citrate showed a melt point at about 152 degrees C, an identifying fingerprint for the presence of the crystalline form. (D.I. 151 at 602:9-603:9; PTX-546A at fig. 12) A second DSC plot, this one taken from a cyclic experiment (where the temperature was cycled repeatedly between 50 and 300 degrees C), also showed the fingerprint for crystalline fentanyl citrate, just below 150 degrees C. (D.I. 151 at 603:10-604:14; PTX-546A at fig. 20) The DSC plots did not determine the quantity of crystalline fentanyl citrate present.

43. In comparing XRPD results, Bates noted that the magnitude of the peaks generated (at about 6 and 20 degrees 2-theta) were diminished for the 5% dissolved fentanyl citrate in sodium glycolate vis a vis data for fentanyl citrate or sodium glycolate

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[14]"Sonication is where you use ultrasound from a hand ultrasound generator, and it's used very often for mixing [and] for nucleating crystals, crystal growth. It's very good at making crystals grow. We also use it a lot for simulating wet granulation processes." (D.I. 151 at 665:5-11)

alone. (D.I. 151 at 607:12-608:22; PTX-546A at fig. 23) The loss of XRPD signals indicated to Bates that, when fentanyl citrate and SSG combine, they form a solid solution. (D.I. 151 at 608:24-609:11) Bates testified generally that his testing on the binary system of fentanyl citrate and mannitol was indicative of a solid state. (*Id.* at 613:7-18)

44. Another set of experiments on the fentanyl citrate/SSG system, along with a control dry-blended system made with amorphous fentanyl citrate, reaffirmed Bates's conclusion that the fentanyl citrate in the ANDA product is not present in amorphous form. DSC traces on a dry bed of 5% amorphous fentanyl citrate and SSG showed a glass transition event, common to amorphous materials. (*Id.* at 603:10-604:4, 612:9-613:6; PTX-546A at fig. 20, 30, 31) This signal was not present for the wet processed system and, according to Bates, this evidenced that fentanyl citrate and SSG interact to form a solid solution. (*Id.*)

45. The court turns now to Bates's testing of the actual (800 µg) completed ANDA product. Bates's XRPD data collected was consistent over several samples.[15] (PTX-546A at fig. 47) Bates noted peaks for: magnesium stearate (around 2 degrees 2-theta); fentanyl citrate (slightly over 6 degrees 2-theta); alpha- and beta-mannitol (several peaks between 9 and 13 degrees 2-theta);[16] and potassium bicarbonate (slightly over 11 degrees 2-theta). (*Id.*; D.I. 151 at 615:12-616:25) When he

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[15]Bates did not perform DSC on the ANDA tablets. (D.I. 151 at 669:18-670:7) Bates stated that DSC does not have the sensitivity for a complex product. (*Id.*)

[16]Bates testified that the mannitol Watson uses comes in an alpha and beta polymorph; through processing, the alpha begins to convert to beta. (D.I. 151 at 616:9-20)

normalized the data for sample weight, Bates observed ("semi-quantitatively") the amounts of materials showing up on the XRPD patterns. (D.I. 151 at 617:11-18; PTX-546A at fig. 51) There is a significant difference between the magnitude of the peak for fentanyl citrate dry blend and the diminished peaks for fentanyl citrate in the ANDA product. (PTX-546A at fig. 51; 618:1-8) "[B]y eye, you can see the difference in that scale will give you some indication in the difference of the crystalline amount. It is a very approximate indication. Just by eye, you can see the crystalline component is significantly less than what we expect from the specified drug." (D.I. 151 at 618:14-19) Bates performed "semi-quantitative" calculations in this regard and arrived at the less than 15% quantity for crystalline fentanyl citrate in the 800 µg ANDA product. (*Id.* at 619:3-12)

46. The court turns now to the remaining 85%. Bates also determined that none of the excipients present in Watson' s tablet exhibit X-ray diffraction peaks that interfere with the characteristic peaks of the anhydrous or monohydrate fentanyl citrate. (*Id.* at 597:25-598:6; PTX-546A at fig. 4 (SSG), fig. 6 (mannitol), fig. 8 (potassium bicarbonate), fig. 10 (magnesium stearate), fig. 11 (fentanyl citrate anhydrous), fig. 13 (same), fig. 14 (fentanyl citrate hydrate)) Bates arrived at the conclusion that a solid solution is present by process of elimination, noting that: (1) other crystalline polymorphs, if present, would generate additional peaks not seen in the XRPD data; (2) nanocrystals, if present, would generate a broadening of the crystalline peak that is not seen in the XRPD data; and (3) besides crystalline material, nanocrystalline or any polymorphs, the remaining (amorphous) form is not attainable for reasons explained

above (¶¶ 38-39).[17] (D.I. 151 at 620:1-24)

47. In addition to Bates's testimony, Cephalon offered that of a second solid state chemistry expert, Dr. Stephen Byrn ("Byrn").[18] (D.I. 111 at 49-50) Byrn testified that the attractive associations between SSG and fentanyl, and the ability of SSG to absorb dissolved mannitol, serve to maintain fentanyl and mannitol dispersed along the starch glycolate polymer which, after drying, forms a solid solution. (D.I. 151 at 719:14-720:24) More specifically, fentanyl citrate breaks down in water into fentanyl cations and citrate anions. SSG is also an ionized molecule with negatively-charged glycolate groups hooked up to the polymer. When the solution containing fentanyl citrate, mannitol (a neutral molecule) and water hits the SSG and causes the SSG to expand, the fentanyl cations and glycolate anions will attract each other.[19] (*Id.* at 715:20-718:21, 721:1-2) Byrn then testified that he reviewed Bates's reports and figures and independently concluded, based on this data, that the ANDA product contains a solid solution containing fentanyl citrate, SSG and mannitol. (*Id.* at 721:23-723:6)

(2) Weight of Bates's binary systems data

48. Watson argues that Cephalon did not meet its burden of proof on infringement because Bates has only supported his opinion that a solid solution is

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[17]On cross examination, Bates phrased his theory in terms of three "prime indicators," discussed in more detail *infra.* (D.I. 151 at 645:1-648:12)

[18]Byrn has focused much of his career on the solid state chemistry of drugs. (D.I. 151 at 715:3-8)

[19]In addition to many other associations that are occurring, for example, non-bonded interactions between molecules. (D.I. 151 at 718:22:719:2)

present in the ANDA product by a process of elimination and a "semi-quantitative" analysis. Put another way, as Bates admits, there is no affirmative evidence of a solid solution, only that 15% of the fentanyl citrate of the ANDA product is **not** in solid solution. (*Id.* at 619:3-16)

49. As discussed above, Bates performed extensive experiments on two binary systems: fentanyl citrate and mannitol; and fentanyl citrate and SSG. Bates admitted that he did not produce these combinations in a manner consistent with Watson's process; it is his opinion that he did not need to because he had the actual ANDA product to test. (*Id.* at 664:7-8; 665:22 ("It was not my intent to reproduce the process at all.")) Bates focused on "bracketing" the most critical process step of wet granulation, whereby the mannitol and SSG dry blend is granulated with fentanyl citrate solution. (PTX-162; D.I. 151 at 664:14-18) Bates, however, did not report results for the tertiary system of fentanyl citrate and mannitol and SSG together, as are present (with water) in Watson's granulator. (*Id.* at 661:12-23) What results from Watson's pre-mixing step is a mixture of mannitol and SSG, not fentanyl citrate and either compound. (PTX-162) The fentanyl citrate solution is separately prepared with fentanyl citrate and water before granulation. (*Id.*) Thus, Bates' binary systems do not truly "bracket" the granulation step by representing the products entering into that manufacturing step. Bates did not test a compound representing the four materials in Watson's granulator.

50. Bates's binary system samples were also not prepared in a manner consistent with Watson's process. In Watson's process, prior to granulation, the mannitol and SSG are mixed in a Colette Gral 150 liter mixer for 5 minutes. (PTX-162)

The fentanyl citrate solution is prepared in an isolater for an unspecified amount of time until it is dissolved. (*Id.*) In preparing the binary systems, Bates mixed the compounds (using sonication) for 30 minutes. (D.I. 151 at 665:16-17) Watson's expert, Dr. Adam Matzger ("Matzger"), testified that the sonication process imports more energy than Watson's granulation step and that this energy is "powerful enough to break chemical bonds and actually destroy pharmaceuticals." (D.I. 152 at 859:22-862:11) Moreover, Watson's granulation step is only 17 minutes long.[20] (*Id.* at 665:16-22) For the fentanyl citrate and SSG binary system, Bates used pre-dissolved fentanyl citrate, and more water was added during mixing than is present (by weight) in the Watson process. (*Id.* at 649:18-650:6) ("With respect to the API, we used more water, I think 1.2 or something like that, four times the water.") For the mannitol-fentanyl citrate binary system, Dr. Bates admitted that he did not use the same amount of water as the ANDA process (although he could not recall specifically the amount). (*Id.* at 662:11-664:2) In view of the foregoing, Bates's binary system data does not appear to directly correlate to a particular moment in the actual Watson process.

51. The single-compound and binary system data is relevant, however, because Bates utilized this data to cast light upon the XRPD plots obtained for the actual ANDA product. Specifically, Bates compares the strong peak obtained for dry powder (crystalline) fentanyl citrate with the subtle peak obtained around the same (approximately 6.5 degrees 2-theta) location for the ANDA product. (PTX-546A at fig.

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[20]Notably, the Watson process flow diagram provides that the granulation step occurs for a "total 15" minutes. (PTX-162) At trial, counsel represented that it was 17 minutes.

51) It is this comparison that leads directly to Bates's "semi-quantitative" calculation that 15% of the fentanyl citrate in the ANDA product is crystalline. (D.I. 151 at 617:11-619:16)

(3) Watson's evidence regarding the ANDA product

52. There is no post-trial motion to exclude Bates's testimony as unreliable under *Daubert*. The issue presented, however, bears substantial similarity to a Rule 702 inquisition and Watson cites to *Daubert* caselaw in support of its argument that the court should not appropriate significant weight to Bates's opinions. (D.I. 120 at 23) Watson emphasizes that Bates's methods cannot be reproduced (and validated) by most other persons of skill in the art and that his methodology was not subject to peer review. (*Id.* (citing *In re Paoli R.R. yard PCB Litig.*, 35 F.3d 717 (3d Cir. 1994))

53. During cross examination, Bates characterized his methodology for determining whether a solid solution is present as a factor of three "primary indicators": (1) looking at the analytical patterns of the signal components from the binary system; (2) comparing the measurements of the solid form with (1) above; and (3) determining whether there are any new properties. (D.I. 151 at 643:23-648:12)

Bates admits that, with respect to these indicators,

> [h]ow to use them for interpreting solid solutions is absolutely not known. I think a lot of people would have a hard time taking any of the analytical techniques and coming to any of the conclusions. But there are papers in my own list of publications that explains how to look for the additional feature, how to look for something that is missing, and how to have a patent on that particular approach, and the change in properties is commonly understood as one of the best ways to look for solid solutions[.]

(*Id.* at 660:11-21) Further, "[t]he use of a missing crystalline signal as an indicator of a

solid solution never has been published" by Bates or otherwise. (*Id.* at 679:21-22)

54. The court may properly weigh the qualifications of the expert in adjudging the weight of his opinion. *See In re Paoli*, 35 F.3d at 742 & n.8. Bates appears to be at the very forefront of what is a rapidly evolving field.[21] To this end, that Bates has yet to publish the analytical technique of using a missing crystalline signal as an indicator of a solid solution is not, in the court's view, fatal to his credibility.

55. It is Bates's opinion (based upon the data he collected and discussed *supra*) that the ANDA product contains an amorphous solid solution. There is undisputably no positive (peak) indicator for the presence of an amorphous solid solution.[22] (D.I. 151 at 679:13-20) Despite criticizing Bates's techniques as unreliable, Watson's experts did not put forward an alternative test by which an amorphous solid solution could be affirmatively detected. As further evidence that there may be "no better way," as discussed *infra*, Watson's expert relied on Bates's data to buttress his own opinions. In consideration of all of the foregoing, the court finds Bates's testimony to be credible.

(4) Watson's noninfringement evidence

56. Watson emphasizes that its expert (Matzger) testified that the ANDA product could contain amorphous fentanyl citrate. Matzger testified regarding the concept of polyamorphism, or the ability of a substance to exist in several different amorphous modifications, which may result in different properties. (D.I. 152 at 840:1-7) Matzger

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[21]Bates's extensive c.v. was admitted as PTX-388.

[22]Watson emphasizes testimony that XRPD cannot detect a "solid solution." (D.I. 120 at 15) Bates's testimony in this regard was that the one type of solid solution for which there is a positive test – a "substitutional" solid solution – is not the type of solid solution he asserts is present in the ANDA product. (D.I. 151 at 643:10-19)

testified that, because Bates performed different process steps than does Watson, the court cannot assume that the amorphous form of fentanyl citrate that Bates created is the same amorphous form of fentanyl citrate that may be present in the ANDA product. (*Id.* at 840:8-20) ("So many factors can lead to a change in the outcome of crystallization.") By implication, the lack of a peak in the ANDA product XRPD pattern correlating to Bates's figure 15 of the XRPD pattern for amorphous fentanyl citrate is not necessarily indicative of the absence of other amorphous forms.

57. Bates admitted that, even if amorphous fentanyl citrate were present in the 800 µg ANDA product that he tested, he would not have been able to detect it (at the level of 0.625% by weight fentanyl citrate contained therein). (D.I. 151 at 671:16-672:3) Yet examining Bates's data, Matzger found evidence of amorphous fentanyl citrate in both the SSG/fentanyl citrate binary system and the mannitol/fentanyl citrate binary system.[23] (D.I. 152 at 830:7-834:20 (citing PTX-546A at figs. 3, 19, 30, 31 and DTX-470) (regarding DSC results); *Id.* at 836:4-838:14 (citing PTX-546A at figs. 15, 38) (regarding XRPD results)) More specifically, Matzger testified that he saw a glass transition temperature (or baseline shift) in Bates's DSC data at about 50 °C, the same place it was seen for pure amorphous material. (D.I. 152 at 833:9-834:10; DTX-470)

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[23]Matzger's testimony is, of course, only reliable to the extent Bates's data (and Bates's testimony thereupon) is also reliable. That two scientists at the top of their field could disagree on their reading of "hard" data is, unfortunately, neither surprising nor a rare occurrence in this court. The court is not tasked with deterrnining the scientific "truth" with respect to infringement, to the extent one exists, only weighing the parties' evidence and resolving their business dispute according to established burdens of proof. Consequently, the court does not deem Bates's evidence more or less credible insofar as Matzger also relied upon it but ultimately disagreed as to its import. (D.I. 120 at 22)

Matzger also compared the XRPD patterns for amorphous fentanyl citrate (PTX-546A fig. 15) with that for the fentanyl citrate/mannitol system (*id.*, fig. 38) and concluded that the 6-degree peaks and 19-degree peaks in each of those patterns evidence the presence of amorphous fentanyl citrate. (D.I. 152 at 837:19-838:9)

58. Watson also asserts that, even if the amorphous form of fentanyl citrate is not present (whether due to the instability referenced by Bates or otherwise), there are other forms for that compound to take. For example, Bates confirmed that sequestration (of the drug or pharmaceutical agent) is a molecular arrangement that would result in drug stability. (D.I. 151 at 634:16-21) In Matzger's opinion, the amorphous form of fentanyl citrate is not the only possibility – polymorphic forms of crystals could be present, "any of which could hide either outside of the window or under some of the [XRPD] peaks of the excipients." (D.I. 152 at 839:5-11) This testimony is buttressed by information on Bates's company's website, discussing "numerous examples of amorphous" material including "disordered variants," several examples not "relat[ing] to any of the crystalline polymorphs nor were they due to a true amorphous form." (DTX-1328) Bates stated that it is "highly unlikely" that there exist fentanyl citrate polymorphs beyond the three found during his screen, but admitted that others could exist. (D.I. 151 at 639:25-640:11)

59. Watson's arguments regarding potential amorphous fentanyl citrate or other polymorphs within the 85% fentanyl citrate at issue somewhat misses the point. All that is required for a finding of infringement in this case is that it is "more likely than not" that some quantity, however miniscule, of the 85% non-crystalline fentanyl citrate is a solid solution. Watson did not quantify the amorphous form (or any of the other possible

forms) present in the ANDA product. (D.I. 152 at 830:7-834:20; 837:19-22, 838:8-9, 839:5-11) (*See also* D.I. 120 at 26 (stating that the "reduction in peak intensity **could be** attributed to the amorphous form") (emphasis added)) There is no opinion that the extent to which the amorphous form (or other forms) may be present would preclude **any** amount of solid solution.

60. Watson's most compelling evidence of record is the testimony of Dr. Robert A. Bellantone ("Bellantone"), Watson's expert in the area of molecular diffusion and hydration thermodynamics. A solid solution (under both parties' constructions) requires molecular mixing. Fentanyl citrate, mannitol and SSG will not mix in the dry state. For a solid solution to form, SSG must be hydrated such that it is fully expanded and can provide a medium for the mannitol and fentanyl citrate to move throughout (a "diffusion medium"). (*Id.* at 917:9-918:12) Using his peer-reviewed method,[24] Bellantone opined that the amount of water present in Watson's process, 8.1L in a 30 kg batch, is insufficient to fully dissolve the fentanyl citrate and mannitol and also hydrate SSG to this extent. (*Id.* at 915:7-11, 935:2-937:10) At a minimum, 152L of water – over 19 times the amount present in Watson's process – would be required to support mixing at the molecular level. (*Id.* at 937:18-938:2)

(5) Discussion

61. Both parties presented credible cases through highly qualified and articulate experts. The court finds, however, that the balance tips in Cephalon's favor on the

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[24]Admitted at DTX-201. In short, Bellatone applied the concept of hydration stoichiometry as a way to look at water-excipient interactions. (D.I. 152 at 912:25-913:19)

issue of whether the ANDA product contains a solid solution. As noted above, Watson's primary theory is that the ANDA product contains amorphous fentanyl citrate. Bates is not a formulator and he did not specifically opine as to stabilizing chemistry, but testified that, in connection with his work in solid state characterization of drugs, he has not seen a pharmaceutical with an amorphous pharmaceutical agent that could be stable for a shelf life of two years.[25] (D.I. 151 at 634:22-635:13) The court found Bates's testimony persuasive that the 85% non-crystalline fentanyl citrate cannot be **completely** in amorphous form. The court's conclusion is buttressed by Byrn, who also testified that amorphous fentanyl is highly unstable. (*Id.* at 722:16-17)

62. While the court found Ballantone's testimony credible, it is not inconsistent with a finding that some portion of the 85% noncrystalline fentanyl citrate is in solid solution form. Ballantone testified that there is insufficient water in Watson's product for SSG to hydrate and fentanyl citrate and mannitol to **fully** dissolve, but it is not clear (from a scientific perspective) that a solid solution cannot form in some part, nor did Bellantone's testimony clearly preclude the presence of any quantity of solid solution.

63. Having considered the remaining arguments in the parties' briefs, and in view of the foregoing, the court finds that Cephalon has met its burden to prove that, "more likely than not," some portion of the ANDA product exists in a solid solution, as

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[25]In view of the foregoing, the court found Matzger's testimony amorphous fentanyl citrate appears to be "quite stable" less convincing. (D.I. 152 at 844:15-22, 846:10-17, 847:18-848:8) Watson does not cite to testimony rebutting Bates's regarding the difficulty in forming the amorphous form in the first instance. (D.I. 120 at 26-27) Watson appears to not have a theory as to what form the amorphous fentanyl citrate actually takes in the ANDA product. (D.I. 151 at 27-28 ("[T]he amorphous form that **may exist** in the ANDA products **may** well be different than the one [Bates] created."))

construed by the court.

b. Buffer system

64. Claim 3 also requires that the "buffer system" is capable of "maintaining a significant portion of said pharmaceutical agent in unionized form following dissolution of said pharmaceutical agent." Cephalon asserts that the potassium bicarbonate in the ANDA product is a "buffer system" because it is an amphoteric compound, or one that can be both its conjugate acid and conjugate base. (D.I. 151 at 741:13-743:8) Watson does not take issue with this functionality, only whether potassium bicarbonate may be properly considered as infringing under the proper construction of "buffer system." (D.I. 120 at 37-39) As discussed *supra*, the court declines to limit "buffer system" to an acid/base pair and, therefore, potassium bicarbonate falls within the literal scope of the claims.

c. Conclusion on claim 3

65. For the foregoing reasons, Cephalon has met its burden to prove infringement of claim 3.

3. Claim 32

66. Watson does not present separate noninfringement arguments with respect to claim 32 and, therefore, the court finds claim 32 infringed. As per the court's claim construction discussion *supra* (¶¶ 24-26), the parties agree that the inventors used the terms "buffer" and "buffer system" synonymously in the claims and, therefore, potassium bicarbonate meets the limitation at issue.

4. Claims 54 and 5

67. Both claims 54 and 5 require, through separate terms, that the pharmaceutical agent is segregated from other components of the drug formulation. Claim 54 requires a "solid solution micro-environment within the drug formulation." As explained previously, this term means that the "drug formulation comprises a solid solution containing the drug (pharmaceutical agent) to be delivered. The solid solution is segregated from other component(s) of the formulation." In support of its argument that the ANDA product contains a "solid solution micro-environment," Cephalon relies on Byrn's testimony. (D.I. 111 at 57-58) Byrn testified that Watson's granulation step creates a solid solution micro-environment containing the fentanyl citrate, mannitol and SSG in the granulator. (D.I. 151 at 755:2-13) Potassium bicarbonate is not included in the solid solution. In response, Watson cites Flanagan's testimony that the ANDA process does not result in a solid solution and, therefore, cannot contain a solid solution micro-environment. (D.I. 120 at 39 (citing Tr. 1039:23-1042:2))

68. Neither party devoted significant attention to claim 54 in its post-trial briefing; however, as presented by the parties, infringement of the "solid solution micro-environment" limitation follows the court's finding that the ANDA product contains a "solid solution." Having found for Cephalon on this issue, and in view of Byrn's testimony above which is consistent with the court's construction, the court concludes that Cephalon has demonstrated infringement of this limitation by a preponderance of the evidence.

69. The other limitation disputed by the parties with respect to claim 54 is whether the potassium bicarbonate in the ANDA product "improves absorption of the

[fentanyl citrate]."[26] In the context of the Khankari patent case, the parties agreed that a claim term reciting an "amount . . . sufficient to **increase** absorption" related to the "rate and/or extent" of absorption. (Civ. No. 08-330, D.I. 327 at ¶ 42) Cephalon (unsuccessfully) relied on the ANDA product's bioequivalence to Fentora® as evidence that this limitation was met. (*Id.* at ¶¶ 55-57) Here, in the '981 patent context, the parties do not ask the court to construe "**improves** absorption" and the court applies its plain meaning. Cephalon relies on the testimony of Byrn, who stated that the potassium bicarbonate in the ANDA product neutralizes fentanyl such that the fentanyl is converted to unionized form. (D.I. 111 at 58 (citing D.I. 151 at 744:10-745:16; 756:22-757:9)) The unionized form is "of course, [ ] what allows [fentanyl citrate] to go in **rapidly** into the bloodstream."[27] (D.I. 151 at 744:21-23) (emphasis added) Watson does not address this testimony (or limitation) in its responsive papers. (D.I. 120) The court finds, therefore, that Cephalon has met its burden to prove infringement of claim 54 by a preponderance of the evidence.

70. Claim 5 requires that the dissolution agent provides a "physical barrier" between the pharmaceutical agent and buffer while in storage. The parties have not asked the court to construe "physical barrier" and the court applies its plain meaning.

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[26]Cephalon identifies potassium bicarbonate as the "pharmaceutical ingredient" that is segregated from the micro-environment and which must improve absorption.

[27]Although there is no evidence of record regarding the **degree** to which potassium bicarbonate improves absorption of fentanyl citrate across the oral mucosa, the court is of the opinion that "improves absorption" is satisfied by Byrn's reference to rapid penetration of the oral mucosa, as compared to "increases absorption," which the court previously held requires some nature of comparator by which the presence of an "increase" may be adjudged. (Civ. No. 08-330, D.I. 327 at ¶ 57) Put another way, that Cephalon did not conduct absorption experiments is not fatal to its current claim. (*Id.*)

Cephalon relies on Byrn's testimony that, during the granulation steps in Watson's process, SSG and mannitol form granules that provide a physical barrier between fentanyl citrate and potassium bicarbonate. (D.I. 111 at 54 (citing D.I. 151 at 747:3-24)) Watson asserts that it does not infringe claim 5 insofar as the ANDA product does not contain a solid solution in the first instance. (D.I. 120 at 39) Watson presents no other noninfringement theories. Having found for Cephalon on the issue of whether a solid solution is present in the ANDA product, and in view of Byrn's testimony above, the court concludes that Cephalon has demonstrated infringement of this limitation by a preponderance of the evidence.

5. Conclusion on infringement

71. For the foregoing reasons, the court finds that Cephalon has proven, by a preponderance of the evidence, that claims 3, 5, 32 and 54 of the '981 patent are infringed.

D. Validity

Watson asserts that claims 3, 5, 32 and 54 of the '981 patent are invalid as obvious in view of U.S. Patent No. 2,698,822 to Halpern et al. ("Halpern") in combination with U.S. Patent No. 5,288,497 to Stanley et al. (the "Stanley '497" patent). Watson further asserts that claims 3 and 32 of the '981 patent are obvious in view of Stanley in combination with U.S. Patent No. 4,671,953 (the "Stanley '953" patent), or Oralet®, a commercial embodiment of the Stanley '953 patent. The court addresses these obviousness arguments in turn.

1. Standard

72. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

73. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or

device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

74. "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

2. Claim 3: Stanley '953 and/or Oralet® with Stanley '497

a. Prior art

75. Stanley '953 is entitled "Methods and Compositions for Noninvasive Administration of Sedatives, Analgesics, and Anesthetics." That patent issued June 9, 1987 from an application filed May 1, 1985; Stanley '953, therefore, is statutory prior art to the '981 patent. 35 U.S.C. § 102(b). Stanley '953 discloses a drug formulation incorporated into a candy matrix such that it can be absorbed through the mucosal tissues. (Stanley '953, abstract) The preferred form for administration is a lollipop, which can be administered by a physician or self-administered by a patient.

> [A] suitable drug is dispersed within a carbohydrate mass or other suitable matrix.[28] The drug-containing carbohydrate mass is then given to a patient to suck on so that the drug will be released into the patient's mouth as the carbohydrate mass dissolves. Being lipophilic, a significant portion of the drug is absorbed through the mucosal tissues of the mouth and pharyngeal and esophageal areas. The drug rapidly enters the patient's bloodstream, and importantly, the blood in the veins draining from the mouth and the pharyngeal and esophageal areas passes through a substantial portion of the body (so that the drug can be absorbed) before the blood passes through the liver (where the drug may be inactivated).

(Stanley '953, col. 6:13-26) Whether administered under a physician's supervision or by a patient, the drug-containing matrix can be removed when the desired effect on the patient is achieved – a "dose-to-effect" manner of administration. (*Id.*, col. 4:18-21, col. 4:31-46) The rate of absorption of the drug into the patient's bloodstream can be varied by altering: (1) the choice of matrix; (2) the concentration of the drug; and (3) the sucking technique. (*Id.*, col. 7:41-53; col. 8:1-4) "A matrix that dissolves quickly will deliver drug into the patient's mouth for absorption more quickly than a matrix that is slow to dissolve. Similarly, a candy that contains drug in a high concentration will release more drug in a given period of time than a candy having a low drug concentration." (*Id.*, col. 7:43-47) Stanley '953 has "broad applicability to a variety of sedative, analgesic, and anesthetic agents" including, specifically, fentanyl. (*Id.*, col. 8:25-30)

76. Oralet® was a fentanyl transmucosal drug formulation covered by the '953 patent that was approved for use by the FDA in 1993. (D.I. 151 at 531:13-23) Oralet® was a product of Anesta, which was later purchased by Cephalon. (*Id.*) Oralet® was

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[28]Stanley uses "drug" to denote the pharmaceutical agent to enter the patient's bloodstream through the oral mucosa. In its analysis *infra*, the court will refer to the "pharmaceutical agent" or "drug" consistent with the '981 patent claim at issue.

produced by the "cooked candy" method in either 200 or 400 microgram drug doses. (*Id.* at 532:4-7)

b. Discussion

77. Watson asserts that "[a] person of ordinary skill in the art would have recognized that the solid solutions in Stanley '953 and Oralet® would achieve the solubility results described in [Halpern]," which is asserted in a separate obviousness combination. (D.I. 112 at 22) "Knowing that fentanyl is more easily absorbed in its unionized form, the skilled artisan would look to another Anesta patent, Stanley '497, and its disclosure of the use of buffering agents to promote the unionized drug and increase absorption through the oral mucosa." (*Id.* at 32-33) (citing D.I. 152 at 1014:19-23; D.I. 151 at 522:7-10)) In support, Watson cites to its expert's non-particularized testimony that did not specifically address a motivation to combine the references. (*Id.*) Watson also cites a general statement by Zhang that one of skill in the art would seek to control more pharmaceutical agent in its unionized form. (*Id.*)

78. Aside from failing to proffer a motivation to combine Stanley '953 or Oralet® with Stanley '497 with a reasonable expectation of success, as Cephalon points out, none of these references disclose a "solid solution" as required by claim 3. Watson's only assertion in this regard is that example 1 of Stanley '953 describes the preparation of a "solid solution." (D.I. 112 at 24 (citing D.I. 152 at 1016:16-18)) The cited testimony falls short of establishing that example 1 of Stanley '953 **necessarily** provides a product containing a solid solution, such as is required for inherency. *See Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) ("Inherency .

. . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.") (citation omitted).

3. Claim 3: Halpern in combination with Stanley '497

a. Prior art

79. Halpern is entitled "Cardiac Glycoside Buccal Composition." It issued January 4, 1955 and constitutes prior art to the '981 patent under 35 U.S.C. § 102(b). (DTX-26)

80. The invention of Halpern "relates to solid compositions containing therapeutically active substances. . . present in combination with therapeutically inert ingredients in the form of a solid solution or composition, which can be dissolved in water or aqueous liquids." (Halpern, col. 1:15-22) It was an object of Halpern to convert pharmaceutical agents[29] "into solid tablets which are soluble in water and aqueous liquids and [which] are suitable for use by administration and absorption through the buccal mucosa of the buccal cavity." (*Id.*, col. 1:30-35) According to Halpern,

> therapeutically active substances which are insoluble or difficultly soluble in water and/or aqueous liquids are converted, by mixing them with compounds of the type described hereinafter, into solid compositions, which are capable of being tableted and, when placed in the form of tablets in a buccal cavity, for example in the sublingual space, form a fluid solution with the saliva. The solution thus formed is absorbed by the buccal mucosa, so that the active substances are released directly into the blood stream of the patient.

(*Id.*, col. 1:63-74) The solid solutions of the invention are capable of being diluted and

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[29]The parties articulate no particular distinction between an active "pharmaceutical agent" or drug as disclosed by the '981 patent and a "therapeutically active substance" as described by Halpern.

solubilization of the normally insoluble pharmaceutical agent occurs, promoting the passage of the pharmaceutical agent through the mucosa and rendering a full therapeutic effect. (*Id.*, col. 1:75-col. 2:2)

81. Stanley '497 is entitled "Compositions of Oral Dissolvable Medicaments;" it was filed September 5, 1989 and issued February 22, 1994. (DTX-55) Stanley is prior art to the '981 patent, which was filed October 27, 1999. 35 U.S.C. § 102(b).

82. Stanley '497 is a grandchild (and claims priority in part) to Stanley '953. Stanley '497 was filed as a continuation in part application; its parent was also filed as a continuation in part application claiming priority to Stanley '953.[30] The patents share common inventors who worked for Anesta, which was later purchased by Cephalon. (D.I. 118 at 9)

83. Stanley '497 discloses the oral transmucosal delivery of pharmaceutical agents such as fentanyl.[31] (Stanley '497 at abstract, col. 9:52-53, col. 17:49-52) Stanley states that the administration of certain pharmaceutical agents through the oral mucosal tissues has previously "shown promise" but that acceptable methods have "been elusive." (*Id.*, col. 4:38-42) The relationship between pH and absorption versus solubility was discussed as follows:

> [P]H conditions within the mouth may tend to adversely affect the administration of certain lipophilic drugs by the mucosal administration route. It has been found in the art that administration of drugs through the mucosal tissues generally

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[30]Certain of the cited disclosures of Stanley '497 recited below are common to both patents. In view of the court's prior holding of nonobviousness with respect to Stanley '953, the court need not contrast the disclosures.

[31]Stanley '497 also uses the term "drug" consistently with the term "pharmaceutical agent" used in the '981 patents.

> occurs best when the drug is in the unionized form. Variations in pH affect the percentage of the drug which is unionized at a particular point in time. As a result, the pH conditions within the mouth can limit the effectiveness of certain drugs administered buccally or sublingually in that those conditions cause the drug to exist in the ionized form which is largely unavailable for transfer across the mucosal tissues.
>
> Other potent drugs are substantially nonlipophilic and do not naturally permeate mucosal tissues. Hence it would be a significant advancement in the art of administering potent, fast-acting drugs, if suitable methods and compositions permitted both lipophilic and nonlipophilic drugs to be administered transmucosally.

(*Id.*, col. 4:46-64)

84. The invention of Stanley '497 was also a drug-containing lollipop. Stanley '497 taught that precise control over the dosage and effect of a drug could be obtained by administering the drug transmucosally by sucking a drug-containing dissolvable dosage form having a handle. (*Id.*, col. 5:42-52, col. 21:59-64) The dissolvable matrix on a handle is an effective method for administering potent and fast-acting drugs transmucosally "in a dose-to-effect manner[32] such that sufficient drug is administered to produce precisely the desired effect." (*Id.*, col. 5:19-26) The matrix includes the drug (pharmaceutical agent) and may include other dissolvable ingredients such as carbohydrates, fats, or waxes, and may also include colors and sweeteners. (*Id.*, col. 5:42-52; col. 10:60-col. 11:51)

> Buffering agents and other types of pH control can also be added simultaneously in order to provide for maximum drug efficiency. It will be appreciated that drugs in the unionized form are more readily transported across the mucosal membrane. Therefore, if pH conditions can be adjusted to maximize the

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[32]"According to the present invention, the drug dose is given over a period of time rather than all at once . . . Once a sufficient drug response has been achieved, the patient can simply stop sucking on the dosage form" or it may be removed from the mouth. (Stanley '497, col. 7:32-34)

> percentage of unionized drug available, the effectiveness of the drug is maximized.

(*Id.*, col. 6:36-43) Permeation enhancers are also provided as an important feature of the invention. (*Id.*, col. 6:51-55, col. 10:26-32, col. 12:21-29)

85. Further with respect to the control of pH, Stanley '497 provides as follows:

> It is well known that most drugs are weak acids or weak bases and are present in solution in both the unionized and ionized forms. It has been found that the unionized portion of the drug is usually lipid soluble and can readily diffuse across the cell membrane. The ionized portion, conversely, is often lipid insoluble and in some instances, may not effectively penetrate the lipid membrane of the cell. As a result, drugs in the ionized form are generally inefficient in producing a drug effect on the central nervous, cardiovascular, and renal vascular systems.
>
> Whether a drug exists in the ionized or unionized form is largely dependent upon its pKa, and correspondingly on the pH of the solution. The present invention provides the unique ability to control the pH of the solution and thus the ratio of unionized to ionized form of the drug.

(*Id.*, col. 14:62-col. 15:10) According to Stanley '497, change in pH can be accomplished by incorporating particular buffer systems within the composition, preferably, "a citric acid/sodium citrate system," or a conventional phosphate buffer. (*Id.*, col. 16:13-21) Use of a buffer dramatically improves results and makes "buccal drug absorption a fully feasible and optimal delivery method." (*Id.*) Stanley '497 also provides that "pH may enhance drug permeability by unknown mechanisms [such as] affect[ing] drug molecular configuration[.]" (*Id.* at col. 16:32-39)

b. Discussion

86. The issues presented by the parties are whether Halpern discloses "solid solutions" that were "mixed at the molecular level" as the court has construed the term vis a vis the '981 patent. Halpern used the term "solid solution" but, like the '981 patent,

provided no explicit definition of the term. There is no mention of molecular-level mixing in Halpern and, therefore, Watson's argument is essentially one of inherency.

87. To this end, Watson argues that the examples of Halpern and example 2 of the '981 patent are so similar such as to render equivalent products – formulations containing "solid solutions." Watson emphasizes that Cephalon's expert (Byrn) stated that Halpern's examples, describing co-melting a pharmaceutical agent and polyethylene glycol to form solid solutions, is "just like" example 2 of the '981 patent. (D.I. 154 at 1466:13-20) Inventor Zhang testified that example 2 of the '981 patent creates a "solid solution" as claimed by that patent. (D.I. 151 at 532:17-533:15, 535:14-23, 548:21-549:15) Transitively, therefore, Halpern must also provide for a solid solution as claimed in the '981 patent. In response, Cephalon points out that Byrn testified that Halpern – a 1955 reference – used "solid solution" in a different manner: "[M]ost people would date the concept of molecular level mixing in solid solutions in pharmaceuticals to the Riegelman work in the early 1970s."[33] (D.I. 154 at 1439:18-1440:5, 1474:21-1475:5)

88. Ultimately, it is Watson's burden to demonstrate that the prior art contains each of the limitations of the '981 patent such as may invalidate that patent under 35 U.S.C. § 103(a). The court finds that Watson did not meet this burden to demonstrate that the "solid solution" of Halpern is within the scope of the '981 patent claims as construed by the court. As stated above, disclosure by inherency requires proof that the prior art **necessarily** discloses the unstated limitation. *See Continental Can Co.*

[33]Watson objected during trial that this opinion was beyond the scope of Byrn's expert reports; that objection was not pursued post-trial. (D.I. 112; D.I. 128)

USA, Inc., 948 F.2d at 1269. Watson has provided no scientific evidence (or testimony) regarding the product(s) produced by Halpern's examples. It is unclear, therefore, whether (and to what degree) the Halpern product(s) are molecularly mixed.

4. Claim 54

89. Watson also asserts that claim 54 is invalid as obvious in view of Halpern in combination with Stanley '497. (D.I. 112 at 26-27) In view of the foregoing, Watson has not met its burden to prove obviousness in view of the fact that it has not demonstrated that Halpern necessarily discloses a "solid solution" as required by the claims.

90. Among its other limitations, claim 54 requires that a "pharmaceutical ingredient" (other than the pharmaceutical agent)[34] is segregated from the solid solution micro-environment (which, as construed by the court, is a solid solution containing the pharmaceutical agent to be delivered across the oral mucosa). Claim 54 also requires that a pharmaceutical ingredient improves absorption of the drug.

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[34]As noted previously (*supra* n.6), the '981 patent provides that the "pharmaceutical ingredient" may be a dissolution agent, buffers, or other substance:

> Pharmaceutical ingredients that can be used in the formulation of the present invention may include, but are not limited to, absorbents, buffering agents (such as phosphate buffer, carbonate buffer, tris buffer, tartrate buffer, borate buffer, acetate buffer, or maleate buffer), colorants, flavorants, solvents and co-solvents, coating agents, direct compression excipients, disintegrants, glidants, lubricants, opaquants, polishing agents, suspending agents, sweetening agents, anti-adherents, binders, and capsule diluents, the ingredients may also include anti-fungal preservatives, antimicrobial preservatives, clarifying agents, emulsifying agents, antioxidants, levigating agents, plasticizers, surfactants, tonicity agents, and viscosity increasing agents.

('981 patent, col. 11:25-37)

91. Watson again proffers inherency arguments in support of its position that a solid solution micro-environment is disclosed by Halpern. Watson's expert (Flanagan) opined generally that: (a) excipients (pharmaceutical ingredients) added after making solid solution granules by co-melt but prior to tableting, according to Halpern example 1, would necessarily be separate and outside of the solid solution granules (D.I. 112 at 28 (citing D.I. 153 at 1027:23-1028:14)); and (b) a skilled artisan would want to take the "simplest route to preparing a solid solution without making it unduly complicated" and, therefore, would not add a buffering agent in the solid solution itself in practicing example 1 of Halpern (*id.* (citing D.I. 153 at 1097:24-1098:10)). Aside from these conclusory statements, Watson presents no scientific evidence that this occurs, nor did Watson sufficiently explain why a person of ordinary skill in the art would then be motivated to incorporate a buffering agent from Stanley '497 after the solid solution of Halpern was created. Finally, Watson did not specifically address how the asserted combination discloses that the "pharmaceutical ingredient improves absorption of the drug." (*Id.* at 27 (citing D.I. 153 at 1026:20-25))

5. Claims 5 and 32

92. Watson asserts that claim 5 is invalid as obvious in view of Halpern in combination with Stanley '497. (D.I. 112 at 25) Watson has not met its burden to prove obviousness in view of the fact that it has not demonstrated that Halpern necessarily discloses a "solid solution" as required by the claims. Because it does not disclose a "solid solution," Halpern also does not disclose the required "physical barrier" between the pharmaceutical agent and said buffer. As explained above, Watson has not provided clear and convincing evidence of a motivation to combine Halpern and Stanley

'497 with a reasonable expectation of success.

93. Watson asserts both prior art combinations against claim 32. As discussed above, the court has found that none of the asserted references disclose a solid solution. (*Supra*, ¶¶ 78, 88) As explained above, Watson has not provided clear and convincing evidence of a motivation to combine the references with a reasonable expectation of success.[35]

6. Conclusion on validity

94. The court concludes that Watson has not met its burden to prove that the asserted claims are obvious in view of Halpern in view of Stanley '497, or Stanley '953 and/or Oralet® in view of Stanley '497.

III. CONCLUSION

98. For the foregoing reasons, Cephalon has demonstrated, by a preponderance of the evidence, that Watson infringes claims 3, 5, 32 and 54 of the '981 patent. Watson has not met its burden to prove invalidity of the asserted claims by clear and convincing evidence. Judgment shall be entered for Cephalon.[36]

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[35]The court notes as well that Watson's cited testimony in support of the references' purported disclosure of the "wherein said buffer maintains a pH level such that ionization of said pharmaceutical is controlled by said buffer system" limitation specific to claim 32 is not specific to any asserted prior art reference. (D.I. 112 at 26 (claim chart) (citing D.I. 152 at 1020:1-6) ("[Claim 32 is] just describing the purpose of the buffer system to maintain the ionization of the pharmaceutical agent."))

[36]Concurrently, the court will enter judgment for Watson on the Khankari patents portion of this litigation, which was addressed in the court's memorandum opinion in Civ. No. 08-330.